DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

Date • AUG 24 1999

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From Senior Regulatory Scientist, Regulatory Branch, Division of Programs & Enforcement Policy (DPEP), Office of Special Nutritionals, HFS-456

Subject 75-day Premarket Notification for New Dietary Ingredient

To Dockets Management Branch, HFA-305

New Dietary Ingredient:	vincamine
Firm:	General Nutrition Corporation
Date Received by FDA:	June 30, 1999
90-day Date:	September 28, 1999

In accordance with the requirements of section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on public display in docket number 953-03 16 after September 28, 1999.

Robert J. Moore

Robert J. Moore, Ph.D.

95S-0316

RPT53

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Washington, DC 20204

AUG 24 1999

Ronald Thompson, Ph.D.
Vice President, Product Development
General Nutrition Corporation
300 Sixth Avenue
Pittsburgh, Pennsylvania 15222

Dear Dr. Thompson:

This letter is in response to your letter to the Food and Drug Administration (FDA) dated June 25, 1999, making a submission for a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act). Your letter notified FDA of your intent to market a product containing a new dietary ingredient named vincamine.

21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 21 U.S.C. 342(f)(l)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

FDA has carefully considered the information in your submission, and the agency has concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing vincarnine will reasonably be expected to be safe. Your submission contained the results of several human and animal studies that you assert are adequate to evaluate the safety of ingested vincamine.

The submission contained three papers that you assert provide information on the toxicity of vincamine. Two of the papers report the results of studies of intravenously administered vincamine in mice, rats, rabbits, and dogs. Such studies are of limited usefulness for determining the safety of an orally administered dietary supplement. Moreover, results from these animal studies show that vincamine resulted toxic side effects at some dosages, which included, but were not limited to, fibrillation, vomiting, and dilation of peripheral and eye-ground vessels. Other studies contained in the submission reported side effects (e.g., bradycardia, faintness, thrombosis of an arm vein, tinnitus) in healthy human volunteers who were given vincamine intravenously. However, the submission contains no explanation or data that explain why these potentially serious side effects are not grounds for concluding that orally administered vincamine is not safe.

Your submission also contained the findings of short-term (5 weeks) and subchronic (26 weeks) toxicity studies performed in rats to evaluate the safety of a compound identified as TCV-3B. This substance was, however, described in the paper as a derivative of an alkaloid of *Vinca minor*, although the identity of the compound was not provided. In order to evaluate whether the results of these studies have any relevance to evaluating the toxicity of vincamine, it is important to know, among other facts, what alkaloid TCV-3B is derived from, the relationship of TCV-3B to vincamine, and the type of derivative it is. Absent this information, these studies do not provide data that establish that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe.

Your submission also contained 16 articles that reported the results of one or more studies of vincamine in humans and animals. Six of the studies were conducted in animals using single intravenous or bolus injection protocols, which as discussed above, are of limited usefulness to establishing the safety of orally administered vincamine'. The human studies contained in the submission provide little support for concluding that chronic or long-term consumption of dietary supplements containing this ingredient will reasonably be expected to be safe in healthy people. Many of the studies were conducted to study the pharmacological effects or efficacy of intravenously administered or injected vincamine in sick patients. Moreover, none of the studies submitted were designed nor intended to examine the adverse or toxicological effects of vincamine in healthy people; instead, the dietary ingredient was used as a therapy in studies of persons with serious diseases. Such studies have limited utility for determining whether the long-term use of a substance as an ingredient in dietary supplements is safe because they do not provide dose-response data nor measurements of endpoints of toxicological concern.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that vincamine, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(l)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 33 l(a) and (v).

Please contact us if you have questions concerning this matter.

Sincerely,

Lynn A. Larsen, Ph.D.
Director
Division of Programs and Enforcement Policy
Office of Special Nutritionals
Center for Food Safety
and Applied Nutrition

'One of these studies actually was an in vitro study of cells collected from an animal administered vincamine intravenously. The remaining animal study consisted of a single oral oral bolus dose of vincamine. Those data are not suitable to determining the safety of a dietary supplement containing vincamine.

GNC LiveWell.

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RECEIVED 6/30/99

June 25, 1999

Office of Special Nutritionals
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street (HFS-450)
Washington, DC 20204

Dear Ma'am or Sir:

Pursuant to Section 8 of the Dietary Supplement Health and Education Act of 1994, General Nutrition Corporation ("GNC") located at 300 Sixth Avenue, Pittsburgh, PA 15222 wishes to notify the Food and Drug Administration that GNC will market a new dietary ingredient, Vincamine, a derivative of vinca minor (periwinkle). Accordingly, enclosed please find an original and two (2) copies of this notification.

The dietary supplement which contains Vincamine, will consist of 30mg of Vincamine in a tablet or capsule which will be suggested to be taken one (1) time per day.

Attached please find the scientific studies and other information which estabiish that this dietary ingredient, when used under the conditions suggested in the labeling of the dietary supplement, is reasonably expected to be safe. This information includes:

(1) Product Specification & Process Manufacturing

(2) Toxicity Studies

(3) Clinical Research Study

Very truly yours,

Ronald W. Thompson

Ronald Thompson, Ph.D.
Vice President, Product Development

Enclosures

General Nutrition Corporation, 300 Sixth Avenue, Pittsburgh, PA 15222
Tel: (412) 288-4600